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CASE REPORT

Antiepileptic drugs toxicity: A case of toxic epidermal necrolysis in patient with phenytoin prophylaxis post-cranial radiation for brain metastases

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KEYWORDS

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Cranial radiation

Abstract *Background:* Treatment of epilepsy with antiepileptic drugs (AED) is effective and remains the principal mode of management. A group of adverse effects and drug toxicity can develop immediately or later in the course of treatment. AEDs also have the potential of precipitating idiosyncratic adverse effects including serious cutaneous, hematological and hepatic events. Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe cutaneous adverse reactions are related to or caused by a variety of medications including AEDs, they carry a high mortality and morbidity rate, accurate diagnosis and rapid treatment may improve the prognosis.

Objective: To characterize the clinical features and methods of differentiating Stevens–Johnson syndrome from toxic epidermal necrolysis using a case study and to identify other factors that may contribute to this critical illness.

Conclusion: Clinical knowledge of potential sever adverse reaction of AEDs is essential and may overcome treatment failure with major impact on health-related quality of life in people with epilepsy.

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1. Introduction

Antiepileptic drugs (AED) are known for a variety of adverse reactions. Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS, TEN) are among the severe cutaneous drug reactions reported in the literature that can be initiated by different classes of anticonvulsants, especially in the background of other high-risk factors such as advanced age, malignancy or radiation exposure. Prescribing such medications should be done with caution, especially if the underlying medical condition could increase the risk of developing SJS–TEN.

2. Case presentation

A 45-year-old female presented to the emergency department with progressive non-pruritic macular rash. The rash started on her face and over 3 days spread in a caudal direction to involve her entire body, sparing her legs below the knee (and affecting more than 80% of total body surface area). The rash was vesicular with large bullae on the face and swollen eyes and lips. It was associated with photophobia, a burning sensation in the eyes and visual impairment, dysphagia, dyspnea, and dysuria. These symptoms preceded for 2 weeks duration with prodromal manifestations of fever, malaise, and sore throat.

The patient had been on phenytoin treatment (100 mg tid) for 1 month prior to developing this rash, as a management of secondary partial seizures. She had been diagnosed with brain metastases secondary to breast cancer 2 months earlier and received cranial radiotherapy. The right breast cancer was diagnosed 18 months prior to brain metastases. At that time management included modified radical mastectomy of the right breast followed by 25 sessions of chemo-radiotherapy and tamoxifen hormonal therapy.

In addition to the phenytoin therapy, the patient was on dexamethasone (4 mg bid) and ranitidine (150 mg tid). On admission, physical examination revealed a toxically ill and distressed patient with a temperature of 38.7 °C, pulse rate of 128 beats per minute, blood pressure of 93/57 mmHg and respiratory rate of 18 breaths per minute. Skin examination showed discrete irregular vesicular rash with multiple large bullae on the face extending to the knees with a positive Nikolsky's sign. On the third day of admission, bullae started to slough leaving areas of exposed skin surface (Figs. 1.1 and 1.2). She had edematous lips with necrotic mucus membranes and oral ulcerations. Eyes were also edematous with mucoid discharge. Chest examination showed that the mastectomized right breast scar was hyperpigmented but clear with no evidence of chest wall recurrence. The other breast was normal. Lungs were clear bilaterally with no localizing signs, heart with regular rhythm and no added sounds or gallop rhythm; abdomen was soft, benign with no tenderness or acute findings. No peripheral edema. The neurological exam was unremarkable.

Initial laboratory tests showed a normal white blood cell count and differential, hemoglobin level and platelet count. Serum liver enzymes were abnormal with slightly elevated alanine aminotransferase (81 IU/L) and aspartate aminotransferase (62 IU/L), alkaline phosphatase (71 IU/L), and gamma glutamyl transpeptidase (624 IU/L). Total bilirubin was

Figure 1.1 Left lower limb showed irregular vesicular rash with multiple large bullae.

Figure 1.2 Vesicular rash with bullae started to slough leaving areas of exposed skin surface.

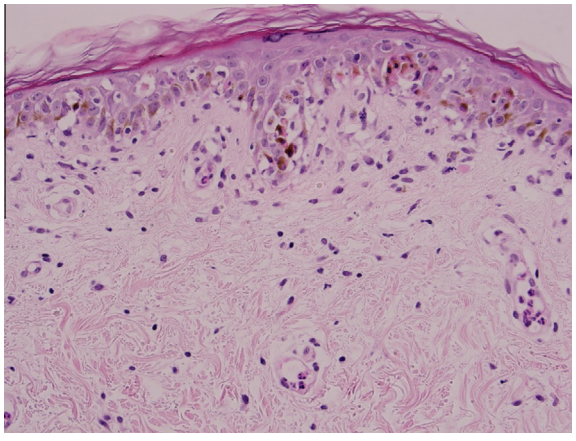

Figure 2.1 (Microscopic description) Section shows epidermal spongiosis, and basal cell hydropic degeneration. Scattered dyskeratotic cells are seen. Mild lymphocytic infiltration of the dermo-epidermal junction is also identified. The upper dermis shows mild edematous change and mild lymphocytic infiltration. The capillary lumina contain neutrophils. No bullae formation is identified.

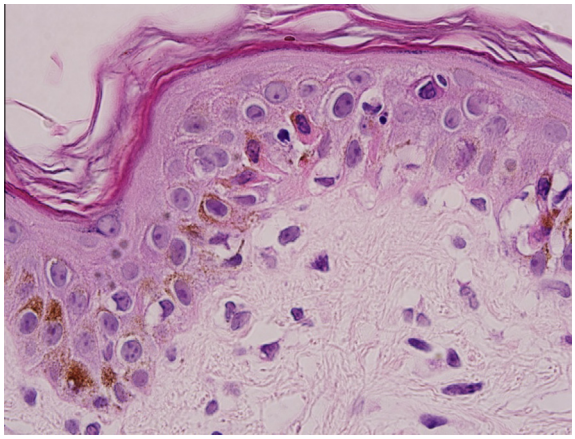

Figure 2.2 (Magnified) Section shows epidermal spongiosis, and basal cell hydropic degeneration. Scattered dyskeratotic cells are seen. Mild lymphocytic infiltration of the dermo-epidermal junction is also identified. The upper dermis shows mild edematous change and mild lymphocytic infiltration. The capillary lumina contain neutrophils. No bullae formation is identified.

7.9 umol/L, total protein 49 g/L, and albumin 22 g/L. Lactate dehydrogenase level was 323 IU/L. Renal function test and serum electrolytes values were normal, i.e., the urea level was 2.8 mmol/L, HCO_3 23 mmol/L and blood glucose level 131 mg/dL. Phenytoin level was 19.5 mg/L. The blood culture revealed gram positive coccemia. There were no signs of phenytoin hypersensitivity syndrome. Skin biopsy was done. Figs. 2.1 and 2.2 depicts the main histopathological changes.

Early on the clinical impression was SJS–TEN with septicemia. The patient was admitted to the intensive care unit and the critical care team, as well as dermatology and ophthalmology, were involved in the patient's management from the start, phenytoin was discontinued immediately, The patient was given aggressive intravenous fluid management, remained in the ICU due to hemodynamic instability (BP: 80/50, PR: 140). She continued to be managed with vigorous IV fluids and inotropic agents hydrocortisone 100 mg IV Q8H, piperacillin–tazobactam 4.5 gm IV Q6H and vancomycin 1 gm IV were administered. Additional therapies included ofloxacin eye drops, itraconazole mouth gel, pantoprazole 40 mg IV Q24H and prophylactic dose of enoxaparin 40 mg daily SQ. Intensive skin care was practiced and dressings were applied. After 2 days in the ICU, the patient showed normalized temperature, but remained dependent on inotropes with deteriorating general condition despite intense medical support and mechanical ventilation support. She manifested repeated episodes of hemodymanic instability until she died on the 11th day of hospitalization.

3. Discussion

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe adverse drug reactions, characterized by low incidence but high mortality. Studies of incidence of SJS and TEN reveal that they are rare diseases with 1–7.1 and 0.4–1.4 cases per million per year in the general population, respectively. The difference in the clinical picture is quantitative: SJS represents cases of less than 10% total body surface area (TBSA) involved; TEN indicates more than 30%; and those in-between are labeled SJS–TEN "overlap". Another important difference between SJS and TEN is the rate of mortality: in SJS it varies from 1% to 5%, in TEN from 25% to 50%. Outcome is difficult to predict. Increasing age, significant comorbidities and a greater extent of skin involvement correlate with a worse prognosis (Lissia et al., 2009). Bastuji-Garin et al. validated a specific TEN severity-of-illness scale (SCORTEN) as a useful method to predict mortality in TEN patients. SCORTEN analyzes seven independent risk factors: (1) age > 40 years; (2) TBSA involved > 10%; (3) serum urea level > 28 mg/dl; (4) glucose level > 252 mg/dl; (5) bicarbonate level < 20 mEq/l; (6) heart rate > 120 beats per minute; (7) presence of cancer/hematologic malignancies. One point is assigned to each risk factor if positive and zero points if negative, with the total representing the final score. A score of 0–1 has an expected mortality of 3.2%; when the score is 2 the mortality rises to 12.2%. It reaches 35.3% and 58.3% when the score is 3 and 4, respectively. Expected mortality is 90% when the score is 5 or more (Bastuji-Garin et al., 2000). Our presented case had multiple risk factors, which made her prognosis very poor. According to the SCORTEN scale, she had a total of 4 positive factors (age > 40, TBSA involved > 10%, HR > 100 and malignancy), corresponding to 58.3% mortality rate.

Drugs have been the most incriminating contributor to the etiology of SJS–TEN, of which anticonvulsants such as phenytoin, carbamazapine, and phenobarbitol are the most commonly implicated. In addition, allopurinol, NSAIDs, corticosteroids and different classes of antibiotics, such as sulfonamides (particularly trimethoprim/sulfamethoxazole), β-lactam, tetracyclines and quinolones (especially ciprofloxacin), were also found to have a role. The correlation between TEN and drug intake is based on clinical recognition and usually develops 1–3 weeks after the administration of the suspect drug. Radiation therapy is another contributory factor (Roujeau et al., 1995; Borchers et al., 2008). Our patient developed symptoms of TEN after 1 month of phenytoin administration and after exposure to cranial radiation.

In 2004, Ahmed et al. reviewed the literature of all published similar cases. They concluded that the need for prophylactic anticonvulsant therapy, especially phenytoin in patients undergoing cranial radiotherapy, should be assessed on a case-by-case basis, stressing phenytoin should be administered with caution and good follow-up (Ahmed et al., 2004).

Diagnosis of the disease is made histologically by skin biopsy (Lissia et al., 2009). The condition usually is preceded by a prodromal phase, which frequently consists of influenza-like symptoms, including fever, cough, myalgias, arthralgias, and malaise, which may last from 1 day to 2 weeks. This is followed by the appearance of skin lesions, mostly on the trunk and face, but can also occur on the neck and proximal extremities. The characteristic skin lesions are flat, irregular, atypical target lesions or diffuse purpuric macules that frequently have necrotic centers (particularly in TEN), and tend to coalesce over the course of time. Lesions can express a positive Nikolsky's sign (lateral displacement of the necrotic epidermis in response to slight pressure). In almost 90% of patients, the mucous membranes are affected; ocular involvement is seen in approximately 60% of patients. Buccal, bronchial, gastrointestinal and anogenital mucosa also have been involved (Borchers et al., 2008). Septicemia is the most

frequent cause of death in patients with TEN and is usually due to *Staphylococcus aureus* or pseudomonas (Atiyeh et al., 2003). The patient in this case study developed the full spectrum of the disease with involvement of all mucus membranes. Her blood culture showed gram positive cocci septicemia which could have added to the poor prognosis.

Optimal treatment of SJS and TEN involves a multipronged, multidisciplinary approach to address the removal of the inciting agent(s), maintaining fluid and temperature homeostasis, treating multi-organ damage, and preventing further systemic complications (Borchers et al., 2008). Since medications are the most common cause of TEN, and most likely SJS as well, it is imperative to take an extensive history to determine and then discontinue all potential causative medications. Prompt withdrawal of the culprit drug is associated with a decreased mortality risk, though immediate results after cessation are not always noted. Supportive therapy is similar to treatment for burn patients, preferably in burn center. Treatment strategies therefore are aimed at providing thermoregulation, fluids and electrolytes, and parenteral nutrition when necessary. In addition, it is imperative to monitor closely for infection to prevent sepsis. If there is pulmonary involvement, mechanical ventilation may be required to correct acute hypoxemia, though in less severe situations, nebulized saline, bronchodilators, and physiotherapy can assist in overcoming damage to respiratory epithelium (Abood et al., 2008). Given the majority of patients have ocular involvement, an ophthalmologist should assess and minimize the risk of eye damage with treatments including topical lubricants/antibiotics and steroid drops (Borchers et al., 2008; Roujeau and Stern, 1994; astuji-Garin S, 1993). In a 2008 study, Schneck et al. found no sufficient evidence of a benefit for any specific treatment including corticosteroids, immunosuppressants (cyclophosphamide, cyclosporin), antitumor necrosis factor-alpha agents, plasmapheresis and intravenous immunoglobulin (IVIG) Schneck et al., 2008. The utility of IVIG treatment remains controversial. The lack of controlled, randomized, comparative trials leaves the debate open.

4. Conclusion

Patients on the phenytoin therapy or other medications which could induce SJS–TEN should be closely followed, especially in the context of underlying malignancy and radiation exposure which might potentiate the toxic adverse reactions of these medications. In addition, patients should be warned about the potential side effects of such medications and to seek medical evaluation if they develop any of these side effects, especially cutaneous reactions. Any of these side effects should be taken seriously with thorough physical examination and high index of suspicion for SJS–TEN.

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